

amount that residual gas space therein does not exceed 10% by volume in terms of the proportion of gas space.

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--44. An aqueous injection preparation of thrombomodulin as claimed in claim 36, wherein the prefilled syringe preparation is characterized in that the aqueous solution of thrombomodulin occupies the syringe container in such an amount that residual gas space therein does not exceed 5% by volume in terms of the proportion of gas space.

Conclude
--45. An aqueous injection preparation of thrombomodulin as claimed in claim 36, wherein the inner diameter of the syringe container is 8.6 mm or less.

--46. An aqueous injection preparation of thrombomodulin as claimed in claim 36, wherein said aqueous solution contains 0.05 to 15 mg/ml of soluble thrombomodulin. A/

REMARKS

It is believed that this application has been amended in a manner that places it in condition for allowance at the time of the next Official Action.

Claims 1-19 have been canceled without prejudice, and new claims 22-46 have been added. Support for claims 22-46 can be found in original claims 1-19, and generally throughout the

specification. It is respectfully submitted that no new matter has been added to the present application.

In the outstanding Official Action, the Examiner noted that an application in which the benefits of an earlier application are desired must contain a specific reference to the prior application as requested by the Examiner, the present specification has been amended to reflect that the present application is a 371 of PCT JP98/04609.

The outstanding Official Action also objected to the abstract. An abstract is submitted with this amendment on a separate sheet.

In the outstanding Official Action, claims 1-19 were rejected under 35 USC §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is respectfully traversed.

As noted above, claims 1-19 have been canceled and new claims 22-46 have been added. New claims 22-32 recite the subject matter of original claims 1-11. It is believed that claims 22-32 have been amended in a manner that obviates the contention that the claims are indefinite for reciting the phrases of "a method for maintaining the quality of an aqueous injection preparation of thrombomodulin" and "maintains the quality". Claims 22-32 are directed to a method for maintaining

an aqueous injection preparation of thrombomodulin in a non-frozen or non-freeze-dried liquid form.

It is believed that claims 22-46 have been drafted in a manner to address the informality cited by the Examiner. Claims 22-46 have been amended to provide antecedent basis for all the recitations set forth in the claims. Moreover, the claims of the present invention have been amended, as thoughtfully suggested by the Examiner, to recite that the buffering components "have" a buffering action.

Claims 22-46 no longer recite the phrases "is filled aseptically in a container", "is filled aseptically in a syringe", "long period of time", and "superior". The phrases have been deleted from the claims. It is respectfully submitted that in light of the present amendment, claims 22-47 are definite to one of ordinary skill in the art.

While the claims have been drafted in a manner to address many of the contentions of the outstanding Official Action, applicants respectfully traverse the rejection that the term "substantial" is indefinite.

As the Examiner is aware, the test of definiteness is whether one skilled in the art would understand the scope of the claims. In fact, the term "substantial" has been held as an acceptable term. *Bausch & Lomb Inc. v. Alcon Labs, Inc.*, 53 USPQ2d 1353 (D.C.N.Y. 1999); *Deering, Milliken & Co. v. Temp-Resisto Corp. et al.* 116 USPQ 386 (D.C.N.Y. 1958). While the

term may be broad, it is respectfully submitted that one of ordinary skill in the art would find the term "substantial" definite.

In the outstanding Official Action, claims 1, 2, 5, 6, 8, 12-15, 18 and 19 were rejected under 35 USC §102(b) as allegedly being anticipated by KUNIHIO et al. This rejection is respectfully traversed.

It is respectfully submitted that KUNIHIO et al. disclose a freeze-dried preparation which is distinct and non-obvious from the claimed invention. The invention is easily differentiated from KUNIHIO et al. in that the claimed invention is capable of being in a non-frozen or non-freeze-dried liquid form yet is stable and capable of maintaining its activity.

While the Official Action stated that KUNIHIO et al. disclose a phosphate buffer component and surfactant (KUNIHIO et al., column 98, lines 43-48), KUNIHIO et al. actually disclose that in a pharmacological test, in administration of thrombomodulin into rats, thrombomodulin is dissolved in phosphate buffer immediately before administration.

Thus, KUNIHIO et al. fail to disclose or suggest that an aqueous solution of thrombomodulin can be stored or transported without losing its activity or without change of appearance or turbidity of the thrombomodulin solution when stored for a long term or when shaken.

Furthermore, applicants traverse the Official Action's statement that the aqueous solution of thrombomodulin also has a surfactant (LUBROL™). Specifically, KUNIHIO et al. state in column 9, lines 43-49, "Lubrol (0.005%) was added to the solution in case of "human placental thrombomodulin" for the purpose of solubilization. Thus, applicants submit that there is no teaching that the surfactant is added to soluble thrombomodulin, i.e., TM1. Human placental thrombomodulin is not soluble but rather insoluble.

KUNIHIO et al. disclose that human placenta was homogenized in a buffer without surfactant. The homogenized mixture was then centrifuged to collect a precipitate (or insoluble material). The precipitate was suspended in the buffer and then centrifuged again to collect a further precipitate (insoluble material). The precipitate was extracted with buffer containing surfactant (Triton X-100) to obtain a crude extract (solubilized product) (See KUNIHIO et al., column 12, Reference Example). Thus, as can be understood from the method disclosed by KUNIHIO et al., human placental thrombomodulin represents insoluble material.

Thus, it is believed that KUNIHIO et al. never disclose or suggest a preparation which is stored and distributed in the form of the claimed aqueous preparation. Moreover, KUNIHIO et al. never disclose or suggest a composition of the present invention or the claimed ratio of filling the composition

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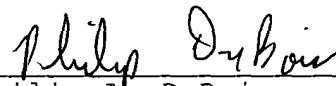
into a syringe. Consequently, it is believed that KUNIHRO et al. fail to anticipate or render obvious the claimed invention.

In view of the present amendment and the foregoing remarks, it is respectfully submitted that the present application is in condition for allowance.

Respectfully submitted,

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By



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